VIRGINIA INHALATION TOXICOLOGY ADVISORY GROUP

MINUTES-UNAPPROVED DRAFT

FIFTH MEETING
July 30, 2009

TIME AND PLACE: 9:00AM – 12:50 PM
DEQ Central Office
629 E. Main Street
Richmond, VA 22469
2nd Floor Conference Room

PRESIDING: Patricia McMurray, DEQ Risk Assessor Program Manager

MEMBERS PRESENT:

Jim Gould, Sierra Club
Chris Bednar, Smurfit Stone
John Morris, Ph.D., University of Connecticut (SOT) – by phone
Debbie Mulrooney, DuPont (VMA) – by phone
Kevin Wallace, M. D., University of Virginia – by phone
Kimber White, Ph. D., Virginia Commonwealth University
Dwight Flammia, Ph.D., Virginia Department of Health

DEQ STAFF PRESENT:

Patty Buonviri, Air Toxics Coordinator (Recorder)
Sonal Iyer, Risk Assessor, Office of Waste Technical Support
Durwood Willis, Office of Remediation Programs Director

GUESTS PRESENT:

Thornton Newland, Virginia Coal Association

Net Connect was used to link those participating by telephone.

The meeting began with VINTAG members, DEQ staff, and guest introducing themselves.

After one correction, a motion was made and seconded to approve the minutes as revised. DEQ staff will post the minutes on the Virginia Town Hall within three days of approval. See http://www.townhall.state.va.us/L/meetings.cfm for the minutes from previous meetings.

ACTION DEQ: One member requested an updated abbreviation list be distributed to each member.

DEQ provided a handout with an updated list of acronyms. A copy of this handout is included as an attachment.

One member inquired about other actions items. DEQ said that the other action items will be discussed during the course of the meeting.

Members were asked to review supplemental information provided by DEQ via email on June 24, 2009 for six chemicals (1,3-Butadiene, Arsine, Chromium VI, Ethylene Dibromide, Hydrogen Sulfide, and n-Hexane) that had been missed during the previous chronic non-cancer review. A copy of the summary sheet for each pollutant is attached.

1,3-Butadiene

One member noted that this is a Class 2A or 2B carcinogen and not a known human carcinogen. One member thought that a calculated risk of 6 in 10,000 is too permissive when you consider it's a carcinogen. Another member states that it may not matter and perhaps we can defer to the cancer number. However, DEQ said that we would still need a chronic non-cancer value to use for the hazard index (HI) since similar effects are additive.

The group agreed to use the EPA number (2 ug/m^3) because it was a more recent review and is a more conservative number since we know it is a carcinogen.

Arsine

Because the difference between Cal EPA and EPA's numbers are less than 3 when considering conventional rounding rules, the process developed by the group for numbers differing by less than three should be applied. The group agreed that Cal EPA's number (0.015 ug/m^3) should be used because it was based on a more recent study and a more recent review.

Chromium VI

One member noted that both EPA and Cal EPA used the same studies for chrome plating workers. One member thought that because of the duration of the study (36 years of data) that a subchronic uncertainty factor of 10 was too large and that EPA's number of 3 seemed like a more reasonable number. However another member mentioned that it is also a carcinogen and may be the driving factor. The group decided that EPA's number makes sense considering the longevity of the study. The group reached consensus to use EPA's number (0.008 ug/m^3).

Ethylene Dibromide

One member noted that ethylene dibromide is an animal carcinogen and that should be considered in making a decision. One member acknowledged that EPA has legitimate concerns but the member would first need to read the study before reaching any conclusions. For instance it's not clear whether the dermal effect was due to contact or not. The member stated that a drop on the skin would result in an affect 10 times greater than if inhaled. The group decided that a copy of the NTP study and Schrader 1988 paper should be obtained and reviewed before a decision could be made.

NEW ACTION DEQ: Obtain studies and distribute to VINTAG members for review.

Hydrogen Sulfide

One member noted that hydrogen sulfide has a low odor threshold. DEQ noted that although hydrogen sulfide was on the original list of hazardous air pollutant under Section 112 of the Clean Air Act, EPA said its inclusion was a mistake and it was removed from the list. However, EPA has been petitioned by various groups to put hydrogen sulfide back on the list.

The group decided that if a number were needed, EPA's number (2 ug/m^3) should be used since their review and the peer-reviewed study used were more recent than Cal EPA's.

n-Hexane

One member pointed out that EPA and Cal EPA used different studies and that both groups used older studies. One member questioned the relevance of the biochemical effect from the 1989 study to humans.

The group decided that DEQ should acquire the studies and make available to the group for review and that the group could discuss in more detail at the next meeting. One member noted that n-hexane is not a carcinogen. Another member suggested considering going to ASTDR to see what value they are using.

NEW ACTION DEQ: Obtain studies and distribute to VINTAG members for review.

One member inquired about hydrogen sulfide since it is not a listed HAP. DEQ stated that they will leave hydrogen sulfide on the list and whether or not it will remain on the list will be addressed during the regulatory process.

15 minute break

Acute/short term values: Irritants v non irritants

Action DEQ: DEQ will request funding for ACGIH documents based on group's recommendation.

DEQ acquired and reviewed ACGIH documents and created a spreadsheet which compares acute values for Cal EPA, Virginia's SAAC, and the ACGHI threshold limit values for the group to review. The spreadsheet also contained a separate page with short term values from Texas, and a page with some new additional acronyms. A copy of the spreadsheet is attached.

DEQ noted that the total number of pollutants contained on the spreadsheet is 326 even though there are only 187 listed hazardous air pollutants under Section 112 of the Clean Air Act. However, some of the named pollutants such as glycol ethers or metal compounds are a group or family of chemicals that could contain hundreds of different chemicals. The spreadsheet contains short-term values for 251 chemicals. Of the 251 values, Cal EPA has values for 51 chemicals and from the ACGIH, 158 have time-weighted averages (TWA), 32 have a short-term exposure level (STEL), and 10 have a ceiling.

DEQ looked at how Cal EPA values compared to the TLVs from the ACGIH. For the 51 chemicals with Cal EPA values, a ratio was calculated (TWA/Cal EPA value or STEL/Cal EPA value or ceiling/Cal EPA value). The average ratios were about 40:1 for TWA, 68:1 for STEL, and 35:1 for ceiling values when compared to the Cal EPA numbers.

DEQ told the group that the DEQ SAAC values are based on ACGIH ceiling or STEL values divided by 40 and the TWA is divided by 20. DEQ also stated that the TWA values are chronic (occupational receptor but long term). The value is intended to establish a safety threshold for a working life and would not be directly applicable for setting short term values. DEQ noted that the STEL and ceiling values would be more appropriate for setting short term values.

DEQ also included on the spreadsheet the basis for the TLV, whether or not the chemical was an irritant, the critical effect (for example, eye irritant or other effect). DEQ pointed out that some chemicals also have a skin reference if skin is the significant exposure route.

One member thought that by looking closely at Cal EPA's values that a methodology may be able to be developed to derive values for DEQ. DEQ noted that ACGIH does not have documentation on how the values were derived even though their review and write up were good, quantitatively it is not as detailed as we would prefer to have.

DEQ also reviewed the derivation of the TLV to see if there was a standard safety or uncertainty factor. DEQ found that there was not and that they varied quite a bit. For

example, many of the chemicals are 1 if a LOAEL was used, for acrylic acid, it was between 2 and 2.5, for chloroform it was 5 times, and for epichlorohydrin 10 times.

One member thought that grouping chemicals by whether or not it is an irritant may help us to derive a value. However, in calculating ratios no difference was seen if the chemical was an irritant or not an irritant. The member also noted that calculating standard deviation doesn't seem to provide any consistency either.

One member suggested that we could just stay with current formula for SAAC unless an analysis has been done.

Currently DEQ derives their values as follows:

TWA/20 (since the TWA is chronic not acute)

STEL and Ceiling/40 for acute.

One member thought that for the chemicals that have a Cal EPA number, we could adopt those because a chemical specific value would be more appropriate where there is one. One member suggested comparing the Cal EPA values with the STEL or ceiling divided by 40 to see how close they are. From the calculations one member did, chloroform seems to be the real outlier. The Cal EPA number is 300 times lower than the TWA value. Also, hydrogen sulfide was another outlier. However, one member thought that might be due the physiologic response to odor which would be a quality of life issue rather than a toxicological effect.

One member suggested taking a geometric mean or a median rather than throwing out the outliers. The median is not influenced by outliers. The member calculated the median to be 17 (for TWA/CalEPA) which is fairly close to the 20 which is currently used by DEQ. This approach may lead us to stay where we are for short term values.

DEQ referred the group to the page of the spreadsheet that contained some short term values from Texas. DEQ did a cursory review of the write ups for the acutes and thought they looked good. Because Texas has some short term values for chemicals that Cal EPA doesn't have, DEQ asked the group whether or not these values should be considered. One member stated that there are other states with some short term values also. After some discussion, the group decided that only values from California should be considered. Another member thought that because this would provide values for only 4 additional chemicals that it would not be worthwhile. The member also noted that Cal EPA and EPA have a transparent method and that we should stick with Cal EPA and EPA to be consistent with the approach taken for the chronic values.

One member proposed using Cal EPA values when available and when not, look at the TLV. The comparison of the TLVs to the CalEPA values show that DEQ's current method provides adequate uncertainty factors for applying an occupational value to the general population.

One member thought that using the STEL/40 seemed like a reasonable approach if a Cal EPA number was not available. The group agreed that the most recent ACGIH values should be used for calculating values and that during the review every four years, if additional Cal EPA numbers are available, the new numbers would be added.

All members agreed to the following process for determining short term values: Use Cal EPA number if one is available. If there is no CAL EPA number, chemicals with either a STEL or ceiling should be divided by 40. If there is no STEL or ceiling, chemicals with a TWA should be divided by 20.

New California Cancer Guidance

DEQ informed the group that in May of 2009 California introduced new cancer guidance. A link to the guidance was provided to VINTAG members. http://www.oehha.ca.gov/air/hot_spots/tsd052909.html The new guidance does not change the unit risk factors but provides a methodology for accounting for susceptibility to carcinogens in early life stages.

EPA also came out with guidance in 2005 which applies an age dependent adjustment factor. EPA's guidance only applies to carcinogens with a mutagenic mode of action. CalEPA applies adjustment factors to all carcinogens. DEQ notes that the Waste Division has been applying a factor for carcinogens with a mutagenic mode of action at risk assessment stage. One member thought we should incorporate the methodology if we want to be consistent with Cal EPA and EPA procedures.

One member stated that unless specific data is available on a particular chemical that we should take the more conservative approach. DEQ states that the unit risk factor will stay the same but the factor would be applied when doing a risk assessment or calculating the SAAC.

One member thought that Cal EPA's approach should be used and the factor applied to all carcinogens. The member noted that the young are always more sensitive. The group reviewed CalEPA's rationale for applying the adjustment to all carcinogens. The group reached consensus to adopt Cal EPA's methodology.

Review of Overall Process and Status

DEQ provided members with a copy of a draft report titled "The Virginia Inhalation Toxicology Advisory Group (VINTAG) Process and Recommendations." DEQ reviewed the report with the members and members provided several suggestions. A copy of the draft report is attached.

For the next and probably final meeting, DEQ stated that the group would review the remaining 2 non-cancer chemicals that were not resolved today and finalize any other outstanding issues.

The next meeting was scheduled for Wednesday, September 9 at 10:00 am.

NEW ACTION DEQ: One member requested the acronym list be updated to include STEL.

Meeting adjourned at 12:50 p.m.

n-HEXANE (110-54-3)

California (2001):

Chronic REL 7000 ug/m^3

Derivative Information:

- Studies—one experimental study and two occupational studies:
    1. experimental—Miyagaki, H. 1967. Electrophysiological studies on the peripheral neurotoxicity of n-hexane. Jap. J. Ind. Health 9(12-23): 660-671.
    2. occupational:
        a. Chang, C. M., Yu, C. W., Fong, K. Y., Leung, S. Y., Tsin, T. W., Yu, Y. L., Cheung, T. F., and Chan, S. Y. 1993. N-hexane neuropathy in offset printers. J. Neurol. Neurosurg. Psychiatry. 56(5):538-542.
        b. Sanagi, S., Seki, Y., Sugimoto, K. et al. 1980. Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int. Arch. Occup. Environ. Health. 47:69:79.
- Study Formats:
    1. experimental—Miyagaki—male SM-A strain mice (10 per group) were exposed continuously to 0, 100, 250, 500, 1000 or 2000 ppm commercial grade hexane (65 to 70 per cent n-hexane with the remainder being other hexane isomers) for 6 days/week for one year.
    2. occupational:
        a. Chang—workers exposed to 80 to 210 ppm hexane (mean of 132 ppm), 20 to 680 ppm isopropanol (mean of 235 ppm), and 20 to 84 ppm (mean of 50 ppm) toluene. The workers worked 12 hours per day for six days per week. The mean duration of employment was 2.6 years, with a range of one month to 30 years.
        b. Sanagi—workers exposed for an average of 6.2 years to solvent vapors consisting of an eight hour time weighted average of 58 ppm (+/- 41 ppm) n-hexane and 39 ppm (+/- 41 ppm) acetone.
- Critical Effects:
    1. experimental—Miyagaki—electromyography, strength duration curves, electrical reaction time, and flexor/extensor chronaxy ratio, gait posture and muscular atrophy were studied. Increased complexity of neuromuscular unit voltages during electromyographic analysis was noted in 0/6 controls, 1/6 in the

100 ppm group, 3/6 in the 250 ppm group, 5/6 in the 500 ppm group, 3/3 in the 1000 ppm group, and 4/4 in the 2000 ppm group. A dose related increase in incidence and severity of reduced interference voltages from muscles was noted in mice exposed to 250 ppm or more, but not in controls (0/6 examined) or in the 100 ppm group (0/6). Dose related abnormal posture and muscle atrophy were noted at 250 ppm or more. This study identifies a NOAEL of 100 ppm for neurotoxicity (68 ppm when adjusted for 67.5% n-hexane).

2. occupational:
    a. Chang—symptomatic peripheral neuropathy was noted in 20 of 56 workers, while another 26 has evidence of subclinical neuropathy. Reduced sensory action potentials; reduced motor action potentials, decreased motor nerve conduction velocity, and increased distal latency were found in most workers.
    b. Sanagi—no overt neurological abnormalities were noted, the mean motor nerve conduction velocity and residual latency of the exposed group were significantly decreased as compared to unexposed workers. The study reports a LOAEL of 58 ppm n-hexane.

- LOAEL—250 ppm
- NOAEL—100 ppm
- Human equivalent concentration—58 ppm (204,740 ug/m^3)
- Uncertainty factors:

1.	LOAEL uncertainty factor	1
2.	subchronic uncertainty factor	1
3.	interspecies uncertainty factor	3
4.	intraspecies uncertainty factor	10
5.	cumulative uncertainty factor	30

US EPA (2005)

RFC **700 ug/m^3**

Derivation Information:

- Study—Huang, J., Kato, K., Shibata, E., et al. 1989. Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. Arch. Toxicol. 63: 381-385.
- Study format—male Wistar rats (eight per group) were exposed to 0, 500, 1200, or 3000 ppm [0, 1762, 4230, 10574 mg/m3] n-hexane (>99 per cent pure) for 12 hours/day, 7 days/ week for sixteen weeks.
- Critical effects—study measured motor nerve conduction velocity in the tail nerve along with body weight before exposure and after 4, 8,12 and 16 weeks to n-hexane, and measured the levels of neuron specific enolase and

beta-S-100. A dose dependant statistically significant reduction in body weight gain was observed in the mid-dose (at 12 weeks) and high-dose (at 8 weeks) rats. There were some neurological deficits in the mid-dose and high-dose, including a reduction in grip strength and a comparative slowness of motion from week 12 of exposure. Among the biochemical changes there were dose dependant reductions in nervous system proteins, particularly the beta-S-100 proteins in tail nerve fibers, which were reduced approximately 75 per cent at all dose levels.

- BMCL—430 mg/m^3
- $BMCL_{ADJ}$—215 mg/m^3
- $BMCL_{HEC}$—215 mg/m^3
- Uncertainty factors:

1.	intraspecies uncertainty	10
2.	interspecies uncertainty	3
3.	less than lifetime uncertainty	3
4.	database uncertainty	3
5.	cumulative uncertainty	300

Discussion:

The California document "Chronic Toxicity Summary—N-HEXANE" contains the following:

"The major strengths of the REL for hexane include: (1) the primary use of an animal study (Miyagaki) with controlled, nearly continuous chronic hexane exposures not confounded by coexposure to other solvents, which observed both a NOAEL and LOAEL; and (2) the results obtained from two different human studies (Sanagi and Chang) which were viewed as being generally consistent with the animal study based REL."

The EPA document "Toxicological Review of n-HEXANE" contains the following:

"…Huang et al. evaluated a comprehensive array of neurological endpoints and an adequate number of animals and exposure groups and was of the appropriate quality for the derivation of the RFC."

Note that CalEPA looked at the Huang study and presumably did not use it because it did not have a NOAEL and the Miyagaki study had a lower LOAEL than the Huang study. (However, U. S. EPA cites 500 ppm as a NOAEL in the Huang study.) U. S. EPA did not discuss the Miyagaki study.

1,3-BUTADIENE (106-99-0)

California (2000):

Chronic REL **20 ug/m^3**

Derivative Information:

- Study—NTP. 1993. U.S. National Toxicology Program. Toxicology and Carcinogenesis Studies of 1,3-Butadiene (CAS No. 106-99-0) in B6C3F1 Mice (Inhalation Studies) (TR No. 434). Research Triangle Park, N.C.: National Institute of Environmental Health.
- Study Format—B6C3F1 mice (70 per sex per group) exposed to concentrations of 1,3-butadiene (0, 6.25, 20, 62.5, 200 or 625 ppm) administered 6 hours per day, 5 days per week for up to two years.
- Critical Effects--two year survival was significantly decreased in mice exposed to 20 ppm and greater primarily due to chemical related malignant neoplasms. Increased incidences of non-neoplastic lesions in exposed mice included bone marrow atrophy, gonadal atrophy (testicular, ovarian and uterine), angiesctasis, alveolar epithelial hyperplasia, forestomach epithelial hyperplasia, and cardiac endothelial hyperplasia. Gonadal atrophy was observed at 200 ppm and 625 ppm for males and at 6.25 ppm and higher for females. This study identified a chronic LOAEL of 6.25 ppm for reproductive toxicity.
- LOAEL—6.25 ppm
- NOAEL—not observed
- BMC_{05}—1.40 ppm
- Human equivalent concentration—0.25 ppm (553 ug/m^3)
- Uncertainty factors:
    1. subchronic uncertainty factor 1
    2. interspecies uncertainty factor 3
    3. intraspecies uncertainty factor 10
    4. cumulative uncertainty factor 30

US EPA (2005)

RFC **2 ug/m^3**

Derivation Information:

- Study—same as above
- Study format—same as above
- Critical effects—same as above
- BMC_{10}—1.0 ppm

- $BMCL_{10\ HEC}$—0.88 ppm (1900 ug/m^3)
- Uncertainty factors:
    1. intraspecies uncertainty 10
    2. interspecies uncertainty 3
    3. database uncertainty 3
    4. extrapolation from below $BMCL_{10}$ 10
    5. cumulative uncertainty 1000

Discussion:

The major influence with respect to the difference between the U.S. EPA RFC and the California REL is with the applied uncertainty factors. Note that CalEPA states that a LOAEL UF is not needed when the BMC approach is used. U. S. EPA states that an extrapolation factor for effect level is applied because the 10% response level used as the POD is an adverse effect level. (The IRIS summary states that EPA is planning to develop guidance for applying an effect level extrapolation factor to a benchmark dose.) In addition, U. S. EPA applied a data base uncertainty factor to account for the absence of a multigenerational study and a developmental neurotoxicity study.

ARSINE (7784-42-1)

California (2008):

Chronic REL 0.015 ug/m^3 as As

Derivative Information:

- Study—Wasserman, G., Liu, X., et al. 2004. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ. Health Perspect. 112(13): 1329-33.
- Study Format—conducted a cross-sectional study of intellectual function in 201 As-exposed children in Bangladesh. Children's intellectual function was assessed with tests drawn from the Weschler Intelligence Scale for Children version III including Verbal, Performance, and Full-Scale raw scores. Children provided urine for arsenic and creatinine and blood samples for blood lead and hemoglobin measurements.
- Critical Effects—after adjustment for sociodemographic covariates such as maternal education, height and head circumference, and waterborne levels of manganese, As in drinking water was associated with reduced intellectual function in a dose dependent manner. Children exposed to water arsenic of >50 ug/l had significantly lower Performance and Full-Scale scores than did children with water As levels <5.5 ug/l. Using the Full-Scale raw score, As water concentrations of 10 and 50 ug/l were associated with decrements ofm3.8 and 6.4 points respectively.
- LOAEL—0.46 ug/m^3 (based on LOAEL of 2.27 ug/l)
- NOAEL—not observed
- Human equivalent concentration—na
- Uncertainty factors:
    1. LOAEL uncertainty factor 3
    2. subchronic uncertainty factor 1
    3. interspecies uncertainty factor 1
    4. intraspecies uncertainty factor 10
    5. cumulative uncertainty factor 30

US EPA (1994)

RFC 0.05 ug/m^3

Derivation Information:

- Studies:
    1. Blair, P., M. Thompson, R., Morrissey, et al. 1990a. Comparative toxicity of arsine gas in B6C3F1 mice, Fisher 344 rats, and Syrian

golden hamsters: System organ studies and comparison of clinical indices of exposure. Fund. Appl. Toxicol. 14(4): 776-787.

2. Blair. P., M. Thompson, M. Bechtold, et al. 1990b. Evidence of oxidative damage to red blood cells in mice exposed to arsine gas. Toxicology. 63(1): 25-34.

- Study format:
    1. Blair 1990a
        - Fisher 344 rats--exposed 8-10 week old Fischer 344 rats (15-16/sex/group) 6 hours/day for 14 consecutive days, and 5 days/week for 4 and 13 weeks. Exposure concentrations were 0, 0,025, 0.5, or 2.5 ppm arsine for the 13 week study and 0, 0.025, 2.5 and 5.0 ppm for the other studies. Duration adjusted concentrations for the 13 week study were 0.014, 0.28 or 1.4 mg/m3 for the low-, mid-, and high-exposure groups respectively. Blood and tissue samples were collected 1 and 3 days after the final exposure for rats exposed over 14 days and four weeks respectively.
        - B6C3F1 mice—exposed 8-10 week old B6C3F1 mice (15-16/sex/group) 6 hours/day for 1 day (females only), 14 consecutive days, and 5 days/week for 13 weeks. Exposure concentrations were 0, 0.025, 0.5 05 2.5 ppm arsine for the 23 week study and 0, 0.5, 2.5 and 5.0 ppm for the other studies. Duration adjusted concentrations for the 13 week study were 0.014, 0.28, or 1.4 mg/m3 for the low-, mid-, and high exposure groups respectively. Mice exposed for a single day were sacrificed 0, 1, 2, 4, or 7 days after exposure to track postexposure recovery. Mice exposed for 14 days were sacrificed 1 or 2 days after the final exposure, whereas mice exposed for 13 weeks were sacrificed 3 or 4 days after final exposure.
        - Golden Syrian hamsters—exposed 8-10 week old Golden Syrian hamsters (15-16/sex/group) to 0, 0.5, 2.5 or 5.0 ppm arsine six hours/day, 5 days/week for four weeks. Blood samples were collected 3 and 4 days after final exposure.

    2. Blair 1990b: B6C3F1 mice (10/sex/group) were exposed to 0, 0.25, 0.5 or 2.5 ppm arsine 6 hours per day, 5 days per week for 13 weeks. Blood samples were collected after 5, 15 and 90 days of exposure, and hematological measurements were made.

- Critical effects: Blair 1990a--microscopic examinations revealed no pathology of the nasal cavity or lower respiratory tract in any of the species studied. Treatment related lesions were noted only in the spleen (all species), liver (mice only), and bone marrow (rats only). No clinical effects were reported in any of the species. Blair 1990b—red blood cell

counts, Hgb concentrations, and HCTs were decreased in the 2.5 ppm animals.

- LOAEL— 1.6 mg/m^3
- LOAEL(adj)— 0.28 mg/m^3
- NOAEL— 0.08 mg/m^3
- NOAEL(adj)— 0.014 mg/m^3
- NOAEL(hec)— 0.014 mg/m^3
- Uncertainty factors:
    1. sensitive subpopulations uncertainty factor 10
    2. interspecies uncertainty factor 3
    3. subchronic and database uncertainty 10
    4. cumulative uncertainty 300

Discussion:

Note that U. S. EPA derived a separate RfC for arsine while CalEPA applies the REL for inorganic arsenic to arsine.

There are three main issues to consider:

The California REL is based upon a human study in drinking water. The EPA RfC is based upon inhalation route employing laboratory animals. The drinking water LOAEL of 2.3 ug/L was converted to an air LOAEL by 2.3 ug/day/9.9 m3/day x 0.5=0.46. This assumes 1 L/day ingestion of drinking water and an inhalation rate of 9.9 m3/day by a 10 year old male and a 50% absorption rate.

The California REL is based on total inorganic arsenic (not speciated). The U. S. EPA RfC is based on arsine. California justifies applying the inorganic arsenic REL to arsine by the following statement. "The metabolism of arsine (As^{-III}), while less studied, appears to progress similarly after its oxidation to arsenite (As^{V}) (sic) and is in part the basis for including arsine in the RELs for inorganic arsenic."

The U.S. EPA defines a NOAEL of 0.08 mg/m^3. However, U.S. EPA also states that significantly decreased RBC counts, hemoglobin (Hgb) concentrations, and hematocrits (HCT) were present in blood collected at 80 or 81 days of exposure in all exposed female rats. Since this would have included the 0.08 mg/m3 group, it is not clear why this was not considered a LOAEL. If 0.08 were a LOAEL, an extra UF of 10 would presumably be applied to the $LOAEL_{hec}$ of 0.014 mg/m^3 (cumulative UF of 1000) and this would result in an RfC of 0.014 ug/m^3 which is essentially the same as the CalEPA REL. The Blair, 1990a paper was consulted. The paper states that repeated exposure to 0.025 ppm (0.014 mg/m^3) produced significant anemia in rats.

CHROMIUM VI
[California—CrO3 as Chromic Acid]
[EPA—Chromic Acid Mists and dissolved Cr VI aerosols]

California (2000):

Chronic REL 0.002 ug/m^3

Derivative Information:

- Study—Lindberg, E. and Hedenstierna, G. 1983. Chrome plating; symptoms, findings in upper airways, and effects on lung function. Arch. Environ. Health 38(6): 367—374.
- Study Format—occupational study: respiratory symptoms, lung function, and changes in nasal were studied in 104 workers (85 males, 19 females) exposed in electroplating plants. Workers were interviewed using a standard questionnaire for the assessment of nose, throat, and chest symptoms. Nasal inspections and pulmonary function testing were performed as part of the study. The median exposure time for the entire group of exposed subjects (104) in the study was 4.5 years (0.1-36 years). Forty-three subjects exposed almost exclusively to chromic acid experienced a mean exposure of 2.5 years (0.2—23.6 years). The subjects exposed almost exclusively to chromic acid were divided into a low exposure group (8 hour TWA below 0.002 mg/m^3, N=19) and high exposure group (8 hour TWA above 0.002 mg/m^3, N=24). Exposure measurements using personal air samplers were performed for 84 subjects in the study on 13 different days. Nineteen office employees were used as controls for nose and throat symptoms.
- Critical Effects—at mean exposures below 0.002 mg/m^3, 4/19 workers from the low exposure group complained of subjective nasal symptoms. Atrophied nasal mucosa were reported in 4/19 from this group and 11/19 had smeary and crusty septal mucosa, which was statistically higher than controls. No one exposed to levels below 0.001 mg/m^3 complained of subjective symptoms. At mean concentrations of 0.002 mg/m^3 or above, approximately one third of the subjects had reddened, smeary, or crusty mucosa. Atrophy was seen in 8/24 workers, which was significantly different from controls. Eight subjects had ulcerations in the nasal mucosa and five had perforations of the nasal septum.
- LOAEL—1.9 ug/m^3
- NOAEL—not observed
- LOAELadj—0.68 ug/m^3
- Uncertainty factors:
    1. LOAEL uncertainty factor 3
    2. subchronic uncertainty factor 10

3. interspecies uncertainty factor 1
4. intraspecies uncertainty factor 10
5. cumulative uncertainty factor 300

US EPA (1998)

RFC 0.008 ug/m^3

Derivation Information:

- Study—same as above
- Study format—same as above
- Critical effects—same as above
- LOAEL—0.002 mg/m^3
- NOAEL—not observed
- LOAELadj-.007 mg/m^3
- Uncertainty factors:
    1. LOAEL uncertainty factor 3
    2. subchronic uncertainty factor 3
    3. interhuman variation uncertainty 10
    4. cumulative uncertainty 90

Discussion:

The major influence with respect to the difference between the U.S. EPA RFC and the California REL is with the applied uncertainty factors. U. S. EPA does not explain why it chose a subchronic UF of 3 rather than the default of 10. U. S. EPA RfC guidance states that "…the amount of exposure in a human study that constitutes subchronic is not defined, and could depend on the nature of the effect and the likelihood of increased severity or greater percent response with duration." U. S. EPA notes that the most significant effects (nasal septum perforation) were observed in workers who experienced peak exposures considerably greater than the TWA. Therefore it is not clear whether the TWA or the peak excursion data are more appropriate for the determination of dose. If the peak excursion data are more relevant, then a higher subchronic UF would not be needed.

Note: California has developed a different REL for soluble hexavalent chromium compounds (except chromic trioxide) of 0.2 ug/m^3. EPA has developed a different RFC for hexavalent dust of 0.1 ug/m^3.

ETHYLENE DIBROMIDE (106-93-4)
[1,2-dibromomethane]

California (2001):

Chronic REL 0.8 ug/m^3

Derivative Information:

- Study—Ratcliff, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., and Hornung, R. W. 1987. Semen quality in papaya workers with long term exposure to ethylene dibromide. Br. J. Ind. Med. 44:317-326.
- Study Format—variable workplace breathing zone airborne exposure (88 ppb geometric average [TWA] exposure with peak exposure up to 262 ppb). Average exposure duration 4.9 years, standard deviation 3.6 years.
- Critical Effects—reproductive toxicity; decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) in human males.
- LOAEL—88 ppb (676 ug/m^3)
- NOAEL—not observed
- $LOAEL_{HEC}$—31 ppb (238 ug/m^3)
- Uncertainty factors:
    1. LOAEL uncertainty factor 10
    2. subchronic uncertainty factor 3
    3. interspecies uncertainty factor 1
    4. intraspecies uncertainty factor 10
    5. cumulative uncertainty factor 300

US EPA (2004)

RFC 9 ug/m^3

Derivation Information:

- Study—NTP (National Toxicology Program). 1982. Carcinogenesis bioassay of 1,2-dibromomethane (CAS No. 106-93-4) in F344 rats and B6C3F1 mice (inhalation study). NTIS no. PB82-181710.
- Study format—male and female Fischer 344 rats and B6CF3 mice (n=50 per sex, species, and exposure group) were exposed to 0, 10 or 40 ppm (0, 77 or 307 mg/m3) 1,2-dibromomethane for 6 hr/day, 5 days/week. The study was designed to assess potential adverse effects of 1,2-dibromomethane following 103 weeks of exposure.

- Critical effects—noncarcinogenic effects were hepatic necrosis (male and female rats), retinal atrophy (female rats), adrenal cortical degeneration (female rats), splenic hematopoiesis (female mice), and inflammation of the nasal cavity (female mice). [Note: High exposure rats of both sexes and female mice exhibited high mortality (80-90 percent) beginning at about 60 weeks, resulting in early termination (between 78 and 91 weeks) of these exposure groups. The low exposure groups were not terminated until the end of the study (104-106 weeks) though the low exposure female mice displayed high mortality (62 per cent) relative to controls (20 per cent mortality). The male mouse study was not considered relevant for derivation of an RFC because of high mortality in control and exposed groups due to complications from urinary tract infections that were not exposure-related.]
- LOAEL—76.8 mg/m^3 (nasal inflammation)
- NOAEL—not observed
- $BMDL_{10\ HEC}$—2.8 mg/m^3 (nasal inflammation)
- Uncertainty factors:
    1. interhuman uncertainty 10
    2. animal to human uncertainty 3
    3. incomplete data uncertainty 10
    4. cumulative uncertainty 300

Discussion:

From the California document "Chronic Toxicity Summary—Ethylene Dibromide" page A-42:

"The strengths of the inhalation REL for ethylene dibromide include the use of human exposure data from workers exposed over a period of years, and the presence of the toxic endpoint (male reproductive system) in several experimental animal species. Major areas of uncertainty are the lack of observation of a NOAEL, the uncertainty in estimating occupational exposure, the potential variability in occupational exposure concentration, and the limited nature of the study (fertility was not actually tested). The database for chronic toxicity of EDB in experimental animals would be enhanced if the proper doses were chosen to determine a NOAEL."

From the US EPA document "Toxicological Review of 1,2-dibromomethane" page 14:

"Ratcliffe, et al. (1987) reported summary air exposure data, but there was moderate dermal exposure that could not be quantified (Schrader et al., 1988). Semen of exposed workers exhibited significantly decreased average sperm count per ejaculate and percentage of viable and motile sperm. There were statistical increases in certain types of morphological abnormalities (tapered heads, absent heads, and abnormal tails) in exposed workers. There was also a significant increase in percentage of subjects with sperm counts fewer than 20 million in exposed workers (21.7 per cent compared to 4.7

per cent in controls). The highly variable inhalation exposures and the confounding dermal exposures preclude the use of this population for the development of an RFC."

HYDROGEN SULFIDE (7783-06-4)

California (2001):

Chronic REL 10 ug/m^3

Derivation Information:

- Study—Chemical Industry Institute of Toxicology. 1983. 90 day vapor inhalation study of hydrogen sulfide in B6C3F1 mice. U.S. EPA, Office of Toxic Substances Public Files. Fiche number 0000255-0. Document number FYI-OTS-0883-0255.
- Study Format—90-day inhalation study in mice (10-12 mice per group) exposed to 0, 10.1, 30.5, or 80 ppm, H2S for 6 hour/day, 5 days/week.
- Critical effects—histopathological inflammatory changes in the nasal mucosa
- LOAEL—112 mg/m^3
- NOAEL—42.5 mg/m^3
- $NOAEL_{HEC}$: 1.2 mg/m^3
- Uncertainty factors:

1.	LOAEL uncertainty factor	1
2.	subchronic uncertainty factor	3
3.	interspecies uncertainty factor	3
4.	intraspecies uncertainty factor	10
5.	cumulative uncertainty factor	100

US EPA (2003):

RFC 2 ug/m^3

Derivation Information:

- Study—Brenneman, K. A., James, R. A., Gross, E. A., and Dorman, D. C. 2000. Olfactory loss in adult male CD rats following inhalation exposure to hydrogen sulfide. Toxicologic Pathology 28(2): 326-333. [Previously based upon: Chemical Industry Institute of Toxicology. 1983. 90 day vapor inhalation study of hydrogen sulfide in B6C3F1 mice. U.S. EPA, Office of Toxic Substances Public Files. Fiche number 0000255-0. Document number FYI-OTS-0883-0255.]
- Study Format—10 week inhalation study of 10 week old male CD rats (12/exposure group) to 0, 10, 42, or 111 mg/m3 H2S for 6 hour/day, 7 days/week.
- Critical effects—nasal lesions of the olfactory mucosa
- LOAEL—41.7 mg/m^3
- NOAEL—14 mg/m^3
- $NOAEL_{HEC}$: 0.64 mg/m^3
- Uncertainty factors:

1.	interspecies uncertainty factor	3
2.	sensitive populations	10
3.	subchronic uncertainty exposure	10
4.	cumulative uncertainty factor	300

Discussion:

From the "Toxicological Review of Hydrogen Sulfide" (EPA/635/R-03/005) page 47:

"*The study by Brenneman et al. (2000) was considered to be the most appropriate for the derivation of an inhalation RFC for several reasons. First, the critical effect (nasal lesions of the olfactory mucosa…) has been reported by other investigators…; second, the effect is consistent with the irritant properties of this gas; third, along with the neurological system, the respiratory system has been reported to be a target organ of H2S toxicity by numerous researchers; fourth, the LOAEL (42 mg/m3) and NOAEL (14 mg/m3) are at lower concentrations than those in the other subchronic studies.*"

U. S. EPA has done the most recent review of hydrogen sulfide. The RfC is based on a more recent study with a lower NOAEL. U. S. EPA also used a full 10-fold uncertainty factor for extrapolation from a subchronic (10 weeks) to a chronic exposure. CalEPA used a 3-fold uncertainty factor for extrapolation from subchronic (90 days) to chronic exposure according to their guidelines (8-12% of estimated lifetime). Note that if the same subchronic uncertainty factor had been applied, the RfC and REL would have been within a factor of 2. The Brenneman et al (2000) study utilized only male CD rats.

List of Acronyms
Virginia DEQ Inhalation Toxicology Advisory Group
July 30, 2009

ACGIH: American Conference of Governmental Industrial Hygienists
ATSDR: Agency for Toxic Substances and Diseases Registry
AEGL: Acute Exposure Guideline Levels
BMC: Benchmark Concentration
BMC_{05}: Benchmark Concentration affecting 5% of population
BMC_{10}: Benchmark Concentration affecting 10% of population
BMD: Benchmark Dose
CAA: Clean Air Act
CAAA: Clean Air Act Amendments
CalEPA: California Environmental Protection Agency
CBD: Chronic Beryllium Disorder
CIIT: Chemical Industry Institute of Technology
CNS: Central Nervous System
CSF: Cancer Slope Factor
DAF: Dosimetric Adjustment Factor
DEQ: [Virginia] Department of Environmental Quality
DNA: Deoxyribonucleic acid
DOH: Department of Health
DOE: Department of Energy
EPA: United States Environmental Protection Agency
EEG:
ET: Extrathoracic
ERPG: Emergency Response Planning Guidelines
HAP: Hazardous Air Pollutant
HEC: Human Equivalent Concentration
HI: Hazard Index
IARC: International Agency for Research on Cancer
IRIS: Integrated Risk Information System
mg/m^3: Milligrams per cubic meter
MF: Modifying Factor
MRL: Minimal Risk Level
LOAEL: Lowest Observed Adverse Effect Level
LRT: Lower Respiratory tract
NOAEL: No Observed Adverse Effect Level
NES: Neurobehavioral dysfunction
NTP: National Toxicity Program
PBPK: Physiologically Based Pharmacokinetic [Model]
POD: Point of Departure
PPRTV: Provisional Peer Reviewed Toxicity Values
PU: Pulmonary
RDDR: Regional Deposited Dose Ratio
REACH: Registration, Evaluation, Authorization and Restriction of Chemical substances
REL: Reference Effect Level
REF:Reference
RGDR: Regional Gas Dose Ratio
RfC: Reference Concentration
SAAC: Significant Ambient Air Concentration
TB: Tracheal/Bronchial
TD: Toxicodynamic
TEEL: Temporary Emergency Exposure Limit
TH: Thoracic

TLV-C: Threshold Limit Value- Ceiling
TLV-STEL: Threshold Limit Value- Short Term Exposure Limit
TLV-TWA: Threshold Limit Value- Time Weighted Average
TLV: Threshold Limit Value developed by the ACGIH
TWA: 8 hour Time Weighted Average
TK: Toxicokinetic
UF: Uncertainty Factor
URT: Upper Respiratory tract
$ug/m^{3:}$ Micrograms per cubic meter
VDH: Virginia Department of Health

Equation Variable Definitions

C: Concentration
C_{avg}: Average Concentration
C_{obs}: Observed Concentration
E: Exposure
D: Dose
T: Time
W: Weight

Excel Attachment re: Air Inhalation Acute SAAC-rel-tlv 07-28-09 version available upon request.